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EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	22

DATE MAILED: 05/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/389,835	Applicant(s) Ruoho et al.
	Examiner Michael Brannock	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 10, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2-28* is/are pending in the application.

4a) Of the above, claim(s) *13, 14, and 19-28* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-12 and 15-18* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Claims 2-28 are pending. Claims 2-12, 15-18 will be examined to the extent that the claims relate to the elected species of invention, i.e. a chimeric Bacteriorhodopsin/β2-adrenergic receptor.

Claims 13, 14, 19-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim, as set forth previously.

Response to Arguments

Withdrawn Rejections:

2. The rejection of claims 2-12, 15-18 under 35 U.S.C. 103(a) as being unpatentable over Popot *et al.*, *Current Opinion in Biotechnology* 6:394-402, 1995, Hoflack *et al., Trends in Pharm. Sci.* 15:7-9, 1994 and Teufel *et al., EMBO Journal, 12(9)3399-3408, 1993*, in view of Okamoto *et al.*, Cell 67(723-730)1991, as set forth in item 10 of Paper 19, is withdrawn in view of Applicant's persuasive argument that Popet *et al.* does not establish that the use of bacteriorhodopsin/GPCR chimeras is well established in the art. U.S. Patent No: 5641650, Turner et al., effective filing date of 3/25/1993, is now being relied upon in the following new rejection.

New Rejections:

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 2-12, 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Popot *et al.*, *Current Opinion in Biotechnology* 6:394-402, 1995, U.S. Patent No: 5641650, Hoflack *et al., Trends in Pharm. Sci.* 15:7-9, 1994 and Teufel *et al., EMBO Journal, 12(9)3399-3408, 1993*, in view of Okamoto *et al.*, Cell 67(723-730)1991.

Popot *et al.* suggest that chimeric constructs of bacteriorhodopsin and of G-protein receptors can be made for the purposes of functional and structural investigations (pg 396 col 1); that bacteriorhodopsin "can be used as a 'bench top' on which to arrange engineered loops that are designed to form binding or catalytic sites (pg 397 col. 2), and that a wealth of data indicates that most of the six loops connecting the transmembrane helices in bacteriorhodopsin can be tampered with to large extents and at least three of them can be cut without preventing refoloding of the proteins (e.g. cytoplasmic loop III, reference 61 Teufel *et al*) (pg 397 col. 2). Further, the use of archaebacteria for recombinant expression of bacteriorhodopsin/GPCRs chimeras is well

established in the art, as disclosed in U.S. Patent No: 5641650, e.g. col 4, L46 . Further, it is old and well established in the art that bacteriorhodopsin is famous as a template to construct three dimensional models of G-protein coupled receptors (GPCRs), see Hoflack *et al., Trends in Pharm. Sci.* 15:7-9, 1994, especially col. 1 of page 7. Teufel *et al.* teach that the protein architecture of bacteriorhodopsin (BR) "suggests the possibility of using BR as a structural scaffold in the construction of biological membranes with new and pre-defined properties by replacing the extra-membrane parts of BR with exogenous polypeptide modules of known function", see col 2 of page 3399. Additionally, Teufel et al. teach that the "structural integrity of loops B/C, CD, D/E, and E/F (E/F is the third cytoplasmic loop) is not a prerequisite of BR function and that the construction of multi functional proteins on the basis of BR as a structural scaffold is a feasible proposition. Loops B/C, CD, D/E and E/F are now clearly identified as prime candidates for future constructions of more complex loop replacements" see the last paragraph of page 3405. Additionally, Teufel *et al.* define what residues are to be considered the third cytoplasmic loop, see Fig 1, which correspond exactly to amino acids 171-179 of the instant SEQ ID NO: 2. Okamoto *et al.* teach that peptides corresponding to the third cytoplasmic loop of a GPCR, e.g. the human β-adrenergic receptor, can activate G- protein, see the Abstract.

Therefore, it would be obvious to one of ordinary skill in the art, with reasonable expectation of success to construct chimeric bacteriorhodopsin/ GPCRs, as taught U.S. Patent No: 5641650 and suggested by Popot *et al.* and Teufel *et al.* using regions that are structurally analogous between GPCRs and bacteriorhodopsin, as is well established in the art (see Hoflack

et al.), particularly that of the third intracellular loop of the human β-adrenergic receptor as taught by Okamoto *et al.* The motivation to do so is provided by Popot *et al.* who teach that bacteriorhodopsin "can be used as a 'bench top' on which to arrange engineered loops that are designed to form binding or catalytic sites (pg 397, col 2) and by Okamoto *et al.* who teach the third intracellular loop of the human β-adrenergic receptor provides for binding and activation of G-proteins, and who also teach the need for further study of the structure and function of the third intracellular loop of the human β-adrenergic receptor as is well appreciated in the art, e.g. see Introduction and Discussion. Further, the construction of a bacteriorhodopsin chimera at amino acids 171-179 (intracellular loop III) is suggested by Teufel who show these residues to define the cytoplasmic loop III, see Figure 2.

Applicant's arguments, as the arguments may relate to this rejection, are addressed below. Applicant argues that the prior art does not suggest the desirability of making the claimed invention. This argument has been fully considered but not deemed persuasive. As set forth above, the motivation to do so is provided by Popot *et al.* who teach that bacteriorhodopsin "can be used as a 'bench top' on which to arrange engineered loops that are designed to form binding or catalytic sites (pg 397, col 2) and by Okamoto *et al.* who teach the third intracellular loop of the human β-adrenergic receptor provides for binding and activation of G-proteins, and who also teach the need for further study of the structure and function of the third intracellular loop of the human β-adrenergic receptor as is well appreciated in the art, e.g. see Introduction and Discussion.

Applicant argues that Popet et al. does not teach that chimeric constructs of bacteriorhodopsin and G-protein receptors can be made for the purposes of functional and structural investigations, and that Applicant can find no mention of chimeric constructs of bacteriorhodopsin and G-protein receptors anywhere in the article. This argument has been fully considered but not deemed persuasive. While it may be true that Popet does not expressly teach bacteriorhodopsin/GPCRs, one of ordinary skill in the art would appreciate that this is what Popet is suggesting in the discussion entitled "Split proteins and Chimeras", beginning on page 395, wherein bacteriorhodopsin and GPCRs are discussed in the context of making split proteins, followed by the explicit teaching that "from a practical point of view, such experiments open the possibility to reconstitute proteins form fragments that come from different origins or carry different modifications for the purpose of functional or structural investigations". Thus, the artisan of ordinary skill appreciates from this discussion that it should be possible to construct chimeras (i.e. either split proteins or traditional fusion proteins) from membrane proteins of different origins, bacteriorhodopsin/GPCRs chimeras being and obvious example because of the well established structural relationship between bacteriorhodopsin and GPCRs (as evidenced by Hoflack et al., for example). As set forth previously, Popot teach that the "split protein" chimera approach can be used as an alternative to the construction of traditional chimeras, but it would be obvious to one of ordinary skill in the art that Popot et al. is extolling the advantages of the chimeric approach, in general, to structure/function analysis of receptors. Never-the-less, U.S. Patent No: 5641650 (Turner et al.), is now being relied on in this rejection to expressly teach

bacteriorhodopsin/GPCRs chimeras, and the desirability of expressing such in halobacteria, see col 8 for example.

Applicant argues that Teufel teach a viral peptide/bacteriorhodopsin chimera, and not a mammalian/bacteriorhodopsin. This argument has been fully considered but not deemed persuasive. The obviousness of producing bacteriorhodopsin/GPCRs chimeras is suggested by essentially each reference relied upon in the rejection: Popot *et al*, Hoflack, and Turner et al., as discussed above, given the well recognized structural relationship between bacteriorhodopsin and GPCRs. Further, Teufel *et al.* teach that the protein architecture of bacteriorhodopsin (BR) "suggests the possibility of using BR as a structural scaffold in the construction of biological membranes with new and pre-defined properties by replacing the extra-membrane parts of BR with exogenous polypeptide modules of known function", see col 2 of page 3399. Okamoto teach the third intracellular loop of the human β-adrenergic receptor provides for binding and activation of G-proteins, and who also teach the need for further study of the structure and function of the third intracellular loop of the human β-adrenergic receptor as is well appreciated in the art, e.g. see Introduction and Discussion.

Additionally, Applicant argues that such a chimera would not be predicted to be expressed in archaebacteria. This argument has been fully considered but not deemed persuasive. Turner et al. provide the teaching of expression of bacteriorhodopsin/GPCRs chimeras in archaebacteria. Turner et al., teach that only a small portion of bacteriorhodopsin need be present for efficient expression of bacteriorhodopsin/GPCRs chimeras in archaebacteria

(see col 4), thus the artisan would not expect that replacement of only the third intracellular loop would be problematic, as Applicant suggests.

Applicant argues that although Teufel et al. teach that the third extracellular loop is defined as residues 171-179 of SEQ ID NO: 2, the construct made by Teufel was cut at residues 172 and 178 instead, thus the artisan would not be motivated to make the required insertion between 171 and 179. This argument has been fully considered but not deemed persuasive. One of ordinary skill in the art appreciates that making the cuts at either 172 and 178 (as in the example) or at 171 and 179 (as in Fig. 1) is simply a matter of routine optimization of operating parameters, absent evidence to the contrary.

Applicant argues that one would not have had the expectation that a chimeric fusion protein would have the functional ability to increase the rate of GTP-GDP exchange on a G-protein *in vivo* as required by claims 4 and 5. This argument has been fully considered but not deemed persuasive. First it is noted that the claims require *in vitro* activity. Second it is Okamoto *et al.* that teach that peptides corresponding to the third cytoplasmic loop of a GPCR, e.g. the human β-adrenergic receptor, can activate G- protein, see the Abstract.

Applicant argues that the teachings of Hoflack do not provide the motivation to replace a portion of intracellular loop three between bacteriorhodopsin and a GPCR. This argument has been fully considered but not deemed persuasive. Hoflack is being relied upon only to establish that the structural relationship between bacteriorhodopsin and GPCRs was well established in the

art. Hoflack teach that bacteriorhodopsin is famous as a template to construct three dimensional models of G-protein coupled receptors (GPCRs).

Applicant argues that Okamoto et al. teach that only the peptide be used for structural and functional studies, and that Okamoto does not motivate one to modify Popet, Hoflack and Teufel. This argument has been fully considered but not deemed persuasive. It is true that Okamoto et al. make the statement that the "peptide provides a focal point for studying the mechanism of ligand-dependent receptor regulation", as pointed by Applicant. However, one of ordinary skill in the art would not construe this statement to be so narrow as to exclude using the peptide as part of a construct. To the contrary, an artisan of ordinary skill would understand this to mean that the authors had identified an important part of the third cytoplasmic loop, and that such could be the focal point for the broader study of the receptor for which it is a part and for the signal tranduction processes with which it is involved. Additionally, Applicant argues that the goal of further characterizing βAR could be accomplished using the relatively simple βIII-2 sequence as a probe. This argument has been fully considered but not deemed persuasive. An artisan of ordinary skill would not accept that Okamoto had provided the final tool for the study of the βAR. To the contrary, Okamoto et al have provide a tool that would lead to the development of additional tools, as is well established in the art.

Conclusion

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

May 10, 2003

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